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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/750,005	12/30/2003	Herbert T. Nagasawa	30451.2USUI	9934

26941 7590 11/15/2006

MANDEL & ADRIANO  
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PASADENA, CA 91101

EXAMINER

HEARD, THOMAS SWEENEY

ART UNIT	PAPER NUMBER
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1654

DATE MAILED: 11/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/750,005

Applicant(s)

NAGASAWA ET AL.

Examiner

Thomas S. Heard

Art Unit

1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 08 June 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-4, 7, 9, 10, 20-22, 25, 26, 33-35, 38, 39, 46, 47, 50 and 51 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4, 7, 9, 10, 20-22, 25, 26, 33-35, 38, 39, 46, 47, 50 and 51 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn. Claims 1-4, 7, 9, 10, 20-22, 25, 26, 33-35, 38, 39, 46, 47, 50, and 51 are pending.

### ***Response to Arguments***

#### ***Claim Rejections - 35 USC § 103***

Applicant's arguments, see page 9-16, filed 6/8/2006, with respect to 35 USC § 103 have been fully considered and are persuasive. The rejection of claims 1-4, 7, 9, 10, 20-22, 25, 26, 33-35, 38, 39, 46, 47, 50, and 51 has been withdrawn.

### **New Grounds of Rejection**

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-4, 7, 9, 10, 20-22, 25, 26, 33-35, 38, 39, 46, 47, 50, and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over:

Shirota FN, DeMaster EG, Shoeman DW, Nagasawa HT, "Acetaminophen-induced suppression of hepatic AdoMet synthetase activity is attenuated by prodrugs of L-cysteine," Toxicol Lett. 2002 Jun 7;132(1):1-8;

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Jonas AJ et al, "Cystine accumulation and loss in normal, heterozygous, and cystinotic fibroblasts," Proc Natl Acad Sci U S A. 1982 Jul;79(14):4442-5; and Bender AS et al, "Characterization of cystine uptake in cultured astrocytes," Neurochem Int. 2000 Aug-Sep;37(2-3):269-76.

Shirota et al teaches the suppression of hepatotoxicity and oxidative stress induced by acetaminophen by the administration of the prodrug of L-cysteine, specifically that of CySSME. Shirota et al teaches that the "hepatoprotection by cysteine generated from a prodrug, however, is due to enhanced GSH synthesis and maintenance of hepatic GSH homeostasis rather than to direct scavenging of the reactive-ACP metabolite by cysteine, see page 5, second column and last paragraph. Shirota et al does not teach the use of the naturally occurring, mixed-disulfide, L-Cysteine prodrug CySSG.

Jonas AJ teaches the administration of CSSG (the same as the Applicant's CySSG) for the induction of Cystine in both normal, heterozygous, and cystinotic fibroblasts. Bender A.S. et al teaches that "*the amino acid cystine is required for maintaining cellular levels of glutathione, a compound which protects cells against oxidative stress and various toxins (Meister and Anderson, 1983). Once taken up by cells, cystine is reduced to cysteine, the rate-limiting precursor of glutathione synthesis (Bannai and Teteishi, 1986).*"

The difference between what is instantly claimed and the prior art is that Bender AJ provides the nexus between the administration of CySSG and the production of GSH for the reduction of oxidative stress with a L-Cysteine prodrug.

It would have been obvious at the time of the instantly claimed invention to substitute CySSG for CySSME for the production of GSH and the reduction of oxidative stress due to the toxic dose of acetaminophen. One would have been motivated to do so given Jonas' teaching that intracellular Cystine production can be induced with the administration of CySSG instantly claimed, and with Bender' teaching that Cystine is converted to cysteine, the precursor to GSH. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

### **Conclusion**

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas S. Heard whose telephone number is (571) 272-2064. The examiner can normally be reached on 9:00 a.m. to 6:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for


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published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TSH

  
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